Riunione annuale congiunta AMD-SID 2022
Il diabete al centro di percorsi innovativi di cura

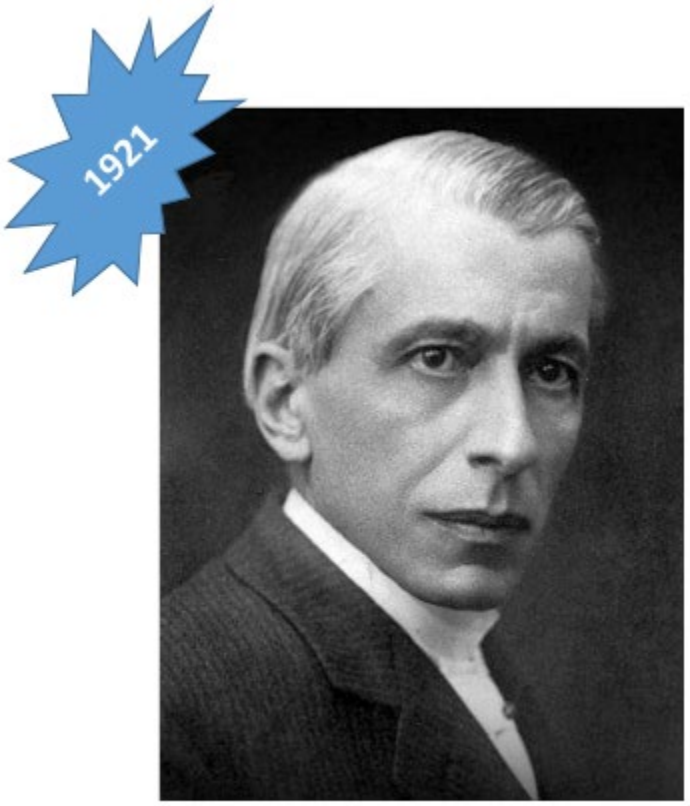
Napoli (NA), 08 ottobre 2022

Il Team diabetologico e la terapia insulinica oggi: luci ed ombre

Sandro Gentile

Università degli Studi della Campania *Luigi Vanvitelli*

Nefrocenter Research Network
Cava dè Tirreni



SCOPERTA DELL'INSULINA

Nicolae Paulescu (1869 –1931)

estrae dal pancreas una soluzione acquosa che, iniettata in un cane diabetico, normalizza i valori di glicemia nel sangue

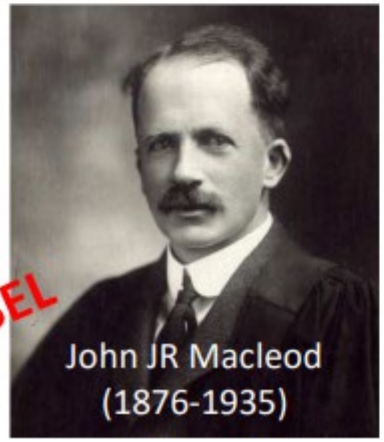
NOBEL

1922

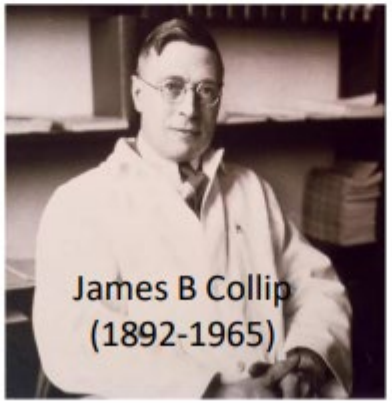
Frederick G. Banting
(1891-1941)

Charles H Best
(1899-1978)

NOBEL



John JR Macleod
(1876-1935)



James B Collip
(1892-1965)

Estrazione da un cane dell'estratto delle isole di Langerhans («isletina»>)

⇩

Iniezione dell'estratto in un cane senza pancreas

⇩

Miglioramento dell'equilibrio glicemico

⇩

Isolamento dell'ormone

IL PRIMO TRATTAMENTO DOCUMENTATO CON INSULINA

SCIENCE'S NEW CURE LEADS HUGHES'S CHILD TO HEALTH

Toronto, Oct. 15.—A gain of six-teen pounds in two months shows the remarkable response of Miss Elizabeth Hughes, fifteen, daughter of Charles Evans Hughes, Secretary of State, to the Insulin treatment for diabetes, which she has been taking here under the personal attention of Dr. F. G. Banting, who discovered the method.

When Miss Hughes came here she was unable to assimilate any of the staple foods which contain carbohydrates, and as a consequence she was forced to a diet which bordered on starvation.

After a few injections of the extract which forms the basis of the treatment, her improvement was marked. These injections provided the element in her blood which oxidized the sugar and after the first week she has been extending her diet until now it embraces almost all foods.

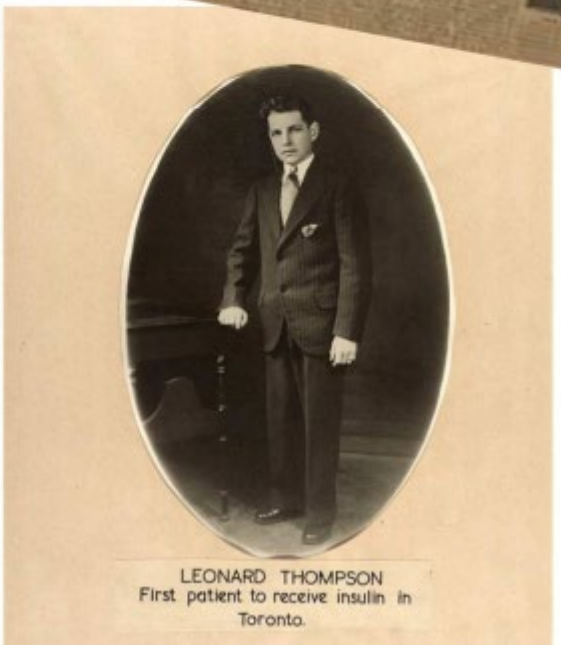
Miss Hughes is making her home in Toronto with a nurse, Miss Burgess, who has been with the Hughes family for some years. Mrs. Hughes visited the city in August, expecting to take her daughter to the Toronto General Hospital, and was overjoyed when she found that this step was unnecessary.

Miss Elizabeth Hughes

THE TORONTO DAILY STAR

TORONTO DOCTORS ON TRACK OF DIABETES CURE

DIABETES SUFFERERS GIVEN MESSAGE OF HOPE



LEONARD THOMPSON
First patient to receive insulin in Toronto.

Nel sito dell'Università di Toronto è possibile vedere i dati storici registrati durante le sperimentazioni.

https://insulin.library.utoronto.ca/about/patients

Le insuline moderne

Frederick Sanger

(1918 –2013)

Determina la sequenza primaria dell'insulina

Le terapie, prima degli anni '80, erano fatte con preparati insulinici industriali ottenuti da pancreas bovini e suini.

Processo costoso e poco efficace:
dal pancreas di un maiale si ricavavano circa 250 UI di insulina, quantitativo sufficiente per circa 6 giorni
(per produrre un flaconcino servivano circa 6 mesi)

Le insuline moderne

Panayotis G. Katsoyannis

(1924 - 2019)

Sintesi in laboratorio dell'insulina umana

Insulin Peptides. XVI. The Synthesis of a Nonapeptide and a Dodecapeptide Derivative Related to the A Chain of Human Insulin (Positions 1–9 and 10–21)[1,2]

Panayotis G. Katsoyannis, Clyde Zalut, and Andrew M. Tometsko

Contribution from the Division of Biochemistry, Medical Research Center, Brookhaven National Laboratory, Upton, New York. *Received April 3, 1967*

Journal of the American Chemical Society / 89:17 / August 16, 1967

Dal 1973 si iniziò a produrre insulina umana

LE PIETRE MILIARI

1936 Hans Christian Hagedorn lavora all'insulina protaminata: insulina NPH, commercializzata nel **1950**

1974 Immissione in commercio delle insuline porcine mono-componenti

1979 Primi pazienti trattati con microinfusori per la terapia insulinica intensiva

1981 insulina umana da DNA ricombinante

1986 Immissione in commercio delle penne con cartucce intercambiabili

1993 Il DCCT dimostra che nel tipo 1 glicemie più basse riducono le complicanze croniche

1996 Immissione in commercio del primo analogo dell'insulina lispro

2000 Analogo sintetico basale dell'insulina umana glargine

2014 Primo biosimilare dell'insulina

2017 analogo ultrarapido aspart

Elliot P. Joslin (1869-1962) conduce regolari cicli di insegnamento per i diabetici fin dal 1016 : *"Il diabetico va a scuola per imparare a preservare la sua vita "*

LA TERAPIA INSULINICA È DA TEAM

GUIDELINES FOR THE DIABETES HEALTH CARE TEAM (Continued)

Professional Responsibilities	Indicate Responsible Professional	Check When Completed	Patient's Responsibilities	Check When Completed
Explain acute complications: – Describe causes, treatment, prevention of hypoglycemia (insulin reaction). – Describe causes, treatment, prevention of hyperglycemia (acidosis). – Provide appropriate literature.			*Learn about acute complications:* – Explain causes, treatment, prevention of hypoglycemia (low blood sugar, insulin reaction.) – Explain causes, treatment, prevention of hyperglycemia (high blood sugar, acidosis). – Read literature (patient and family).	

TEAM

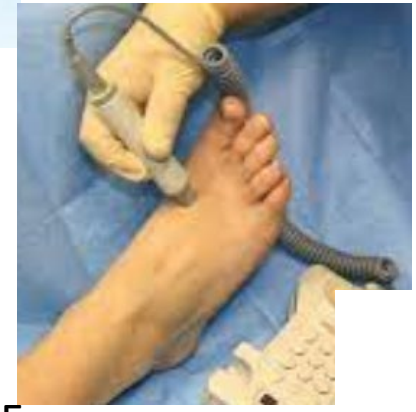

SUPPORTO
Familiari ed amici
Insegnanti
TEAM
Dietista
Infermiere
SOGGETTO DIABETICO
Psicologo
MEDICO CURANTE
DIABETOLOGO
CARDIOLOGO
Assistente sanitario
Altri specialisti
Farmacista
ASSISTENZA

TEAM

ALIMENTAZIONE
STILI DI VITA
CAOUNTING

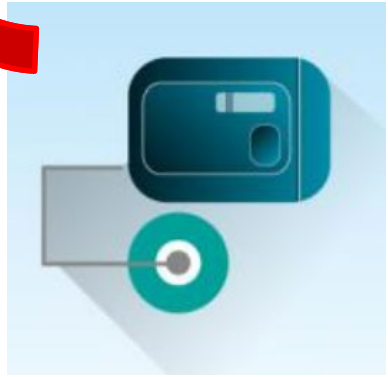
TERAPIA INSULINICA

SCREENING
COMPLICANZE



EMPOWERMENT

MICROINFUSORE



MONITORAGGIO
GLICEMICO

La classifica dei 20 migliori centri italiani

1) Padova U.O. Complessa Diabetologia, Dietologia e Mal. Metab. (tel.049/8216811), Azienda Ulss 16, Univ. Padova e Div. Mal. Metab. (tel. 049/8213061), Policlinico Universitario Sito: www.ulss16.padova.it / www.dmcs.unipd.it
Impact Factor 599,71

20) Genova, Dip. Med. Interna e Specialità Mediche e Dip. Scienze Endocrinol. e Metaboliche, Università di Genova, Az. Osp. San Martino Tel. 010/3537900 www.unige.it
Impact Factor 81,64

Corriere della Sera - La classifica dei 20 **MIGLIORI** centri italiani
https://www.corriere.it › Ospedali_eccellenze › Diabete

CHI TRA VOI LAVORA IN TEAM ?

TEAM ?

Scoperte della 2^ metà del ‘900

Richard Murlin (USA, 1923)	Scopre e definisce il glucagone
William W. Bromer (USA, 1956)	Determina la sequenza primaria del glucagone
Rosalyn Yalow e Solomon Berson (USA, 1959)	Scoprono il dosaggio radioimmunologico
Donald Steiner (USA, 1967)	Scoprono la pro-insulina
Dorothy Hodgkin (England, 1969)	Scopre la struttura tridimensionale dell’insulina
Pierre Freychet (USA, 1971)	Caratterizzano i recettori dell’insulina
Ralph DeFronzo e Reuben Andres (USA, 1979)	Inventano le tecniche di clampaggio dell’insulina
Graham Bell (USA, 1980)	Scoprono la sequenza del gene per l’insulina

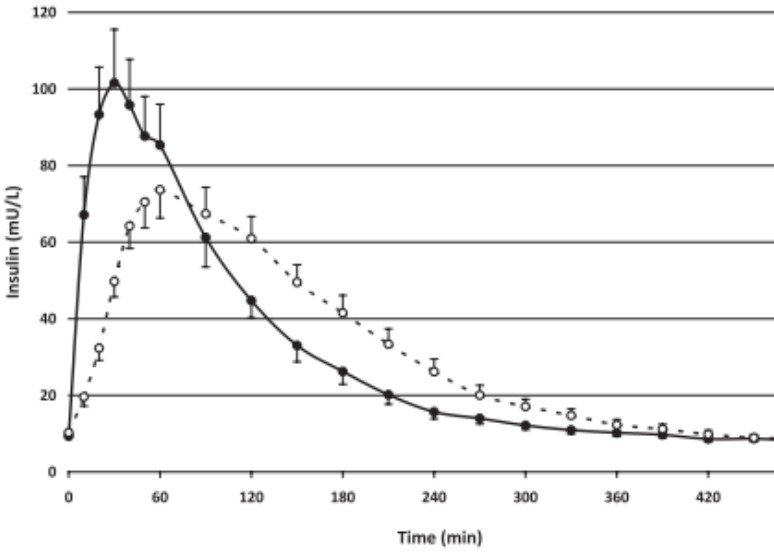
ORIGINAL ARTICLE

Improved Pharmacokinetic and Pharmacodynamic Profile of Rapid-Acting Insulin Using Needle-Free Jet Injection Technology

ELSEMIEK E.C. ENGWERDA, EVERTINE J. ABBINK, CEES J. TACK, BASTIAAN E. DE GALAN,

Diabetes Care 34:1804–1808, 2011

	Jet injector	Conventional insulin pen	*P* value
Pharmacokinetic parameters			
T-INS_{max} (min)	31 ± 3	64 ± 6	<0.0001
C-INS_{max} (mU/L)	108 ± 13	79 ± 7	0.012
INS_{AUC} (unit · min^{-1} · mL^{-1})	14.6 ± 1.6	15.2 ± 1.4	0.53
T-$INS_{AUC50\%}$ (min)	111 ± 5	147 ± 5	<0.0001
Pharmacodynamic parameters			
T-GIR_{max} (min)	51 ± 3	105 ± 11	0.0001
C-GIR_{max} (mg · kg^{-1} · min^{-1})	6.49 ± 0.58	6.09 ± 0.56	0.50
GIR_{tot} (g)	70.0 ± 6.9	83.3 ± 9.8	0.19
T-$GIR_{50\%}$ (min)	123 ± 7	166 ± 6	<0.0001



Lispro administered by the QS-M Needle-Free Jet Injector generates an earlier insulin exposure

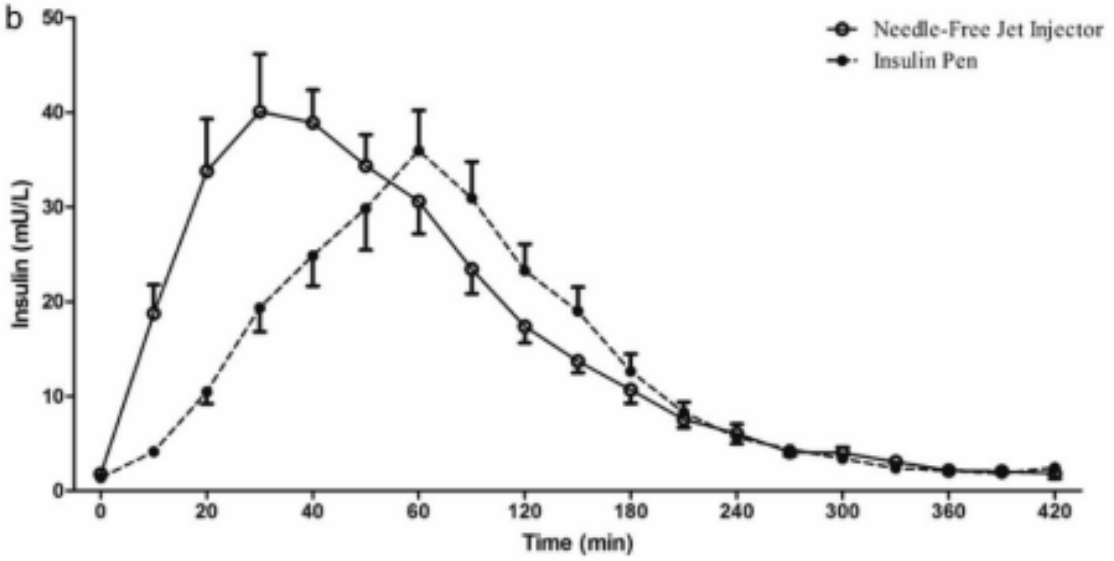
Jinbo Hu, Hui Shi, Changhong Zhao, Xiyue Li, Yue Wang, Qingfeng Cheng, ...show all

Pages 1203-1207 | Received 07 Jan 2016, Accepted 26 May 2016, Accepted author version posted online: 06 Jun 2016, Published online: 17 Jun 2016

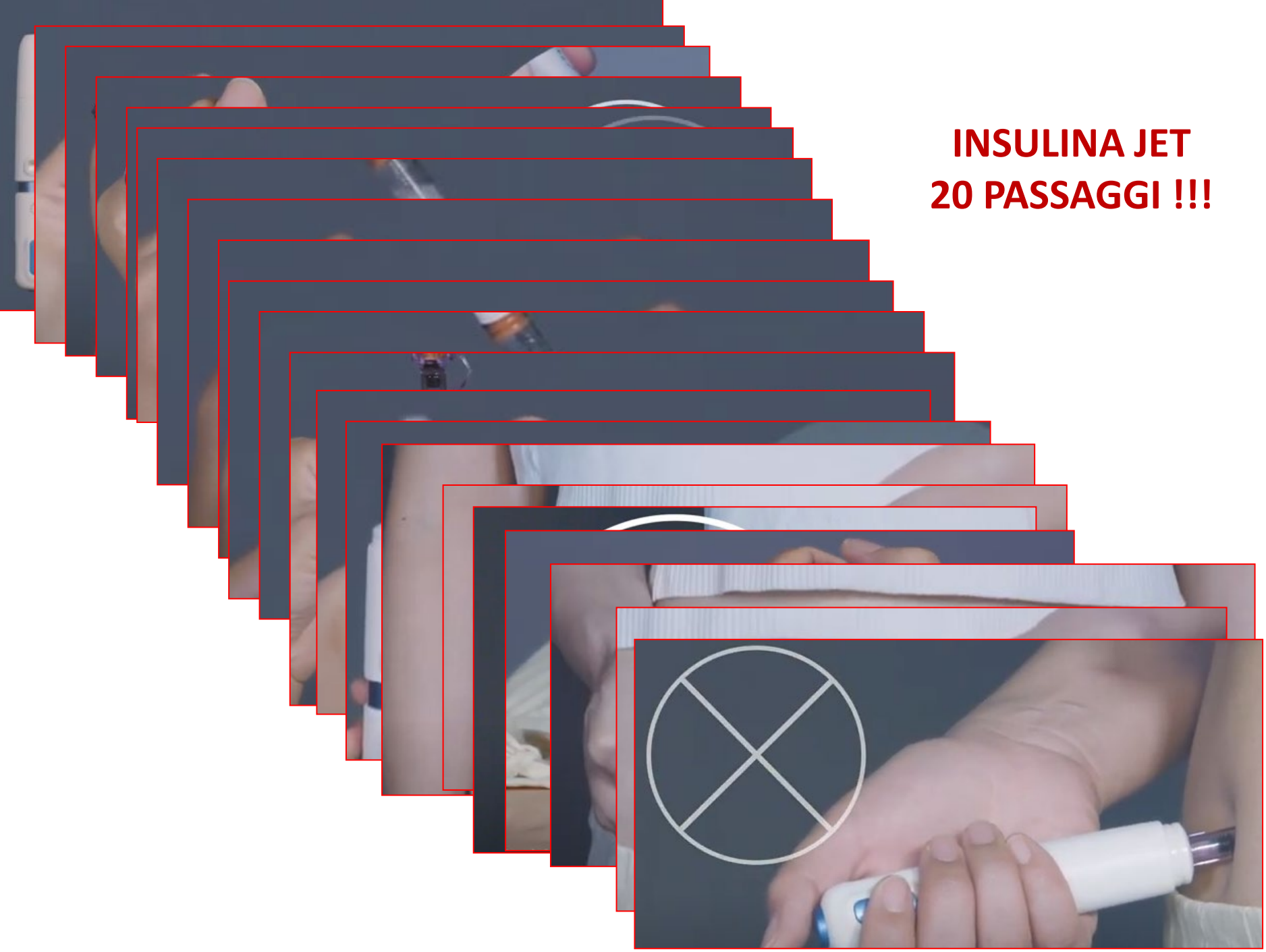
Expert Opinion on Drug Delivery

Volume 13, 2016 - Issue 9

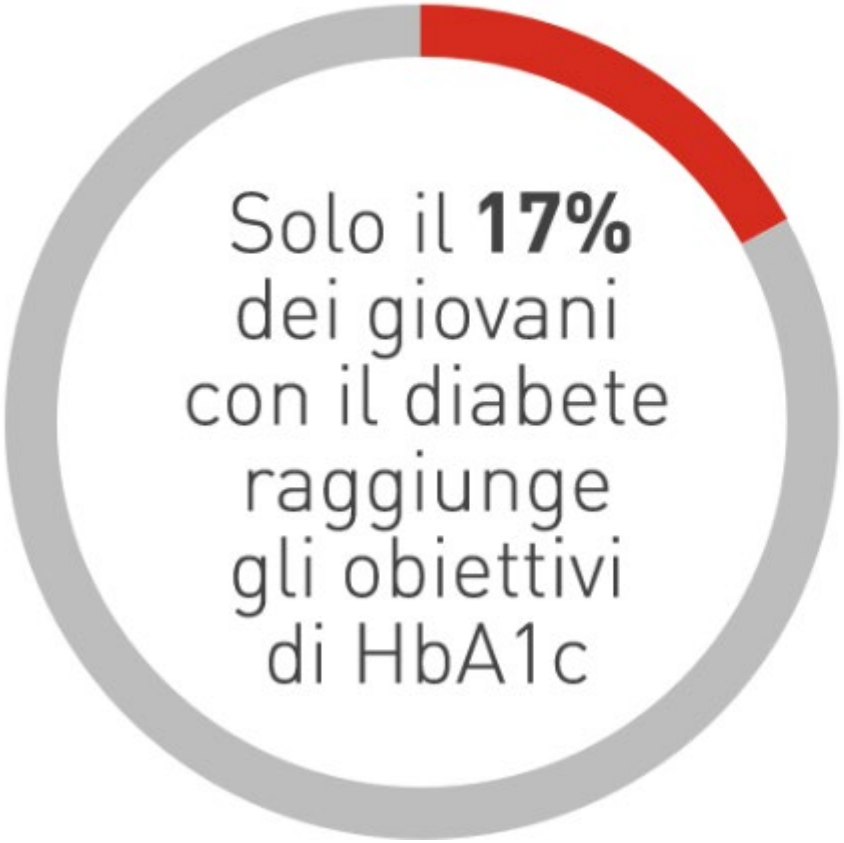
Lispro administered by QS-M needle-free injector results in earlier and higher insulin exposure than conventional pen, and a greater early glucose-lowering effect with similar overall potency

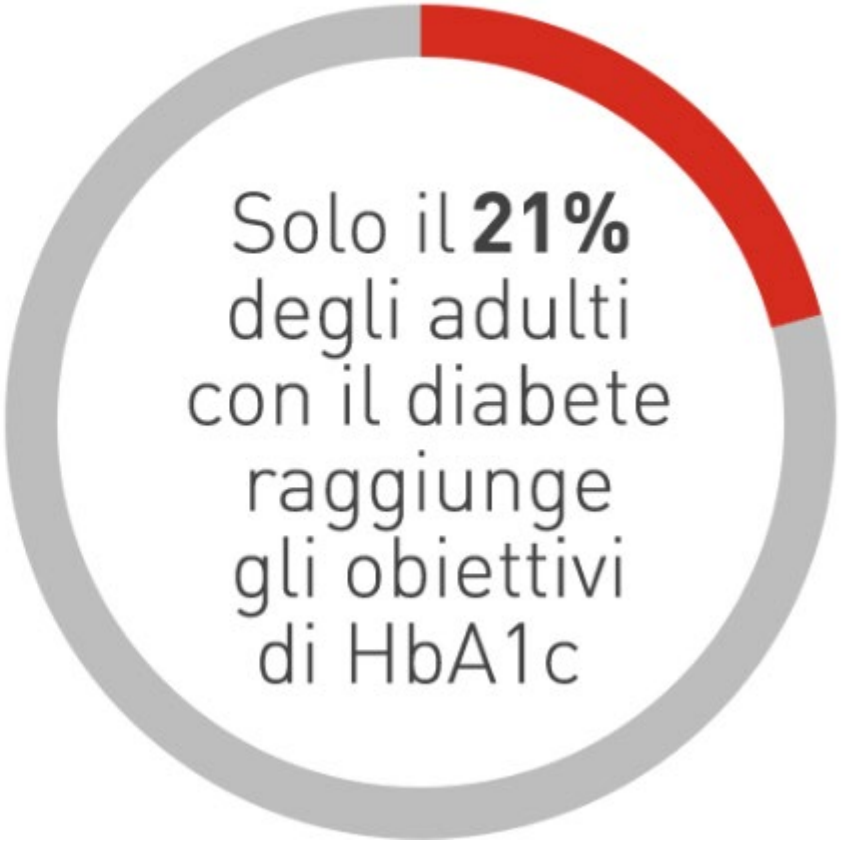


INSULINA JET
20 PASSAGGI !!!

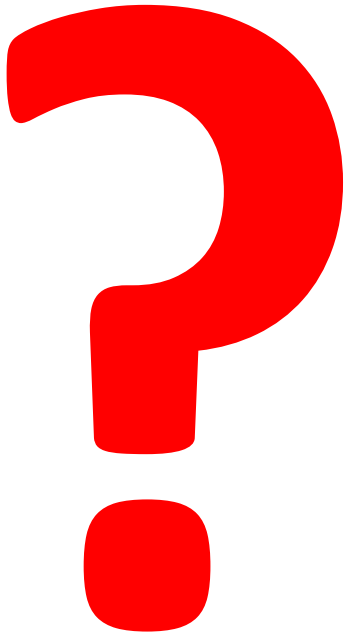


SITUAZIONE GOBALE AL 2019
IN ITALIA TRA 40 E 50%





Foster, Nicole C., et al. "State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016–2018." *Mary Ann Liebert, Inc., Publishers,* 1 Feb. 2019, www.liebertpub.com/doi/10.1089/dia.2018.0384.




Tra il
Dire
e il
Fare

1922

Lipoatrophy following the injection of insulin

Williams J. R.

Journal of Metabolic Research 1922;2:729

PRIMA NOTIZIA DI LIPODISTROFIA

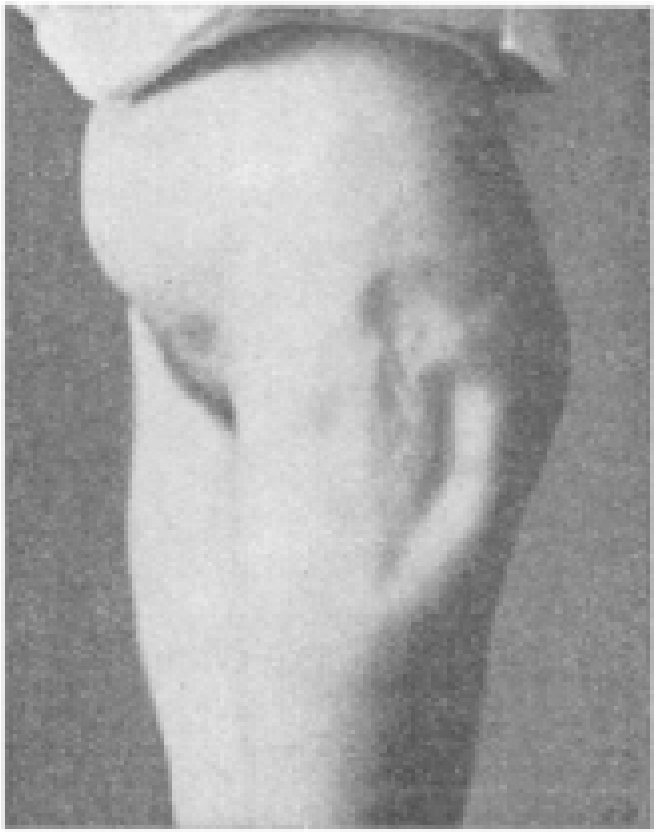
TESTO NON REPERIBILE

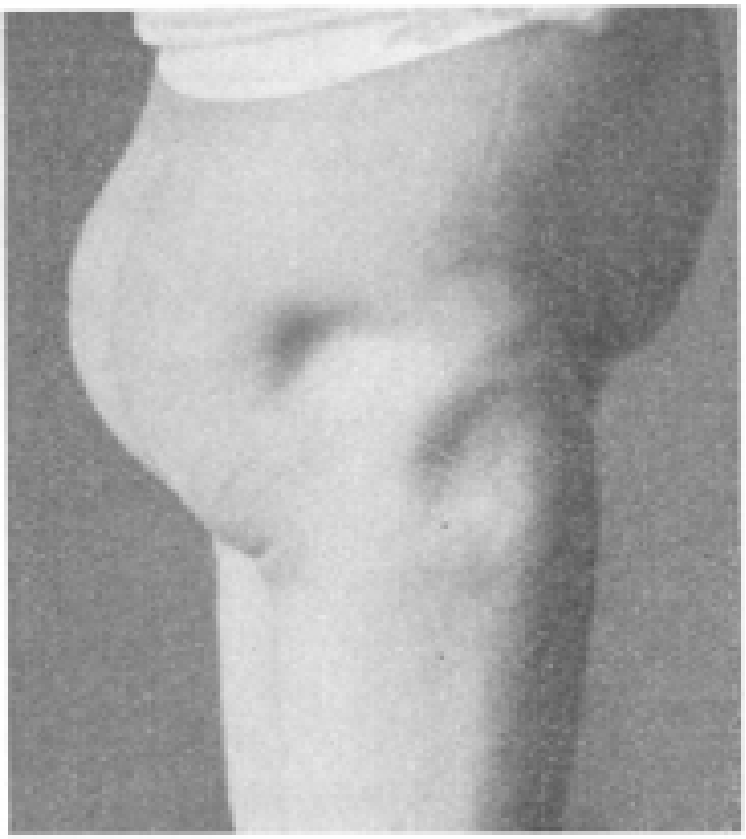
1926

ÜBER LOKALE LIPODYSTROPHIE BEI LANGE ZEIT MIT INSULIN BEHANDELTEN FÄLLEN VON DIABETES*).

Von

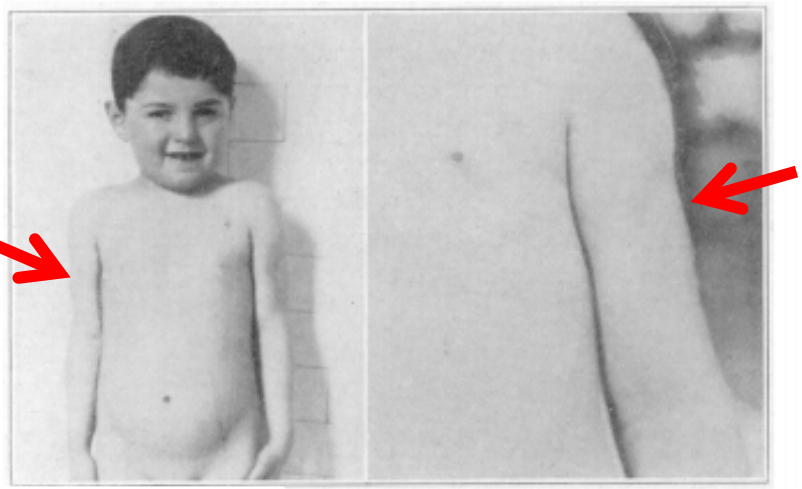
Dr. F. DEPISCH,

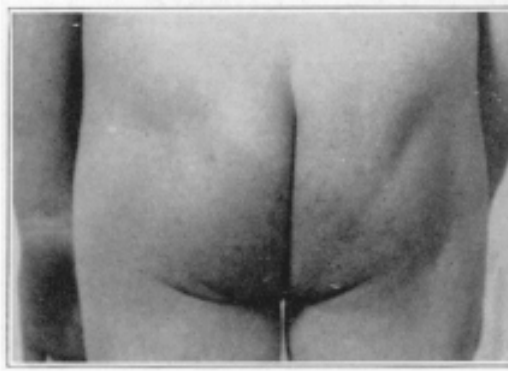


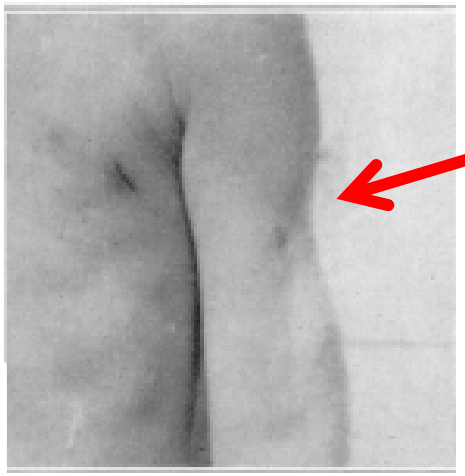


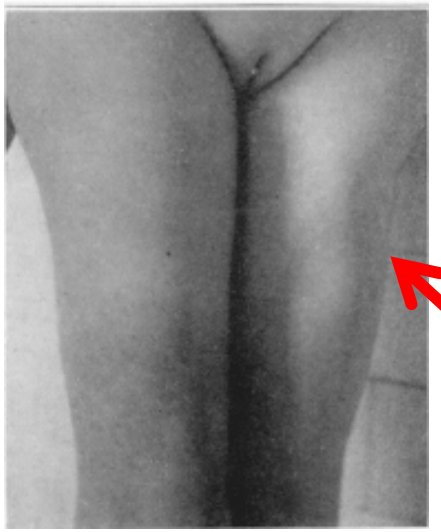
THE FREQUENCY OF ATROPHY OF THE SUBCUTANEOUS FAT FOLLOWING THE INJECTION OF INSULIN *

ALFRED E. FISCHER, M.D.
NEW YORK



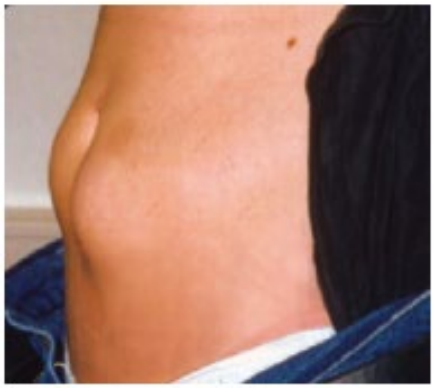






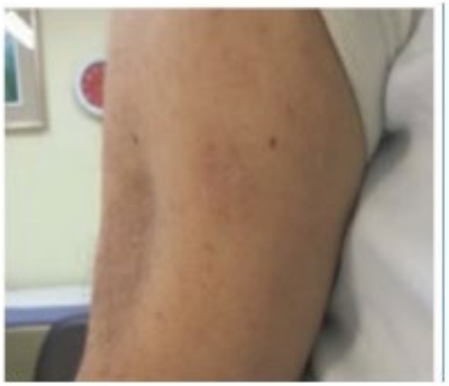
LIPOPDISTROFIA= ALTERAZIONE DELLO STRATO LIPIDICO DEL SOTTOCUTE

LIPOIPERTROFIA

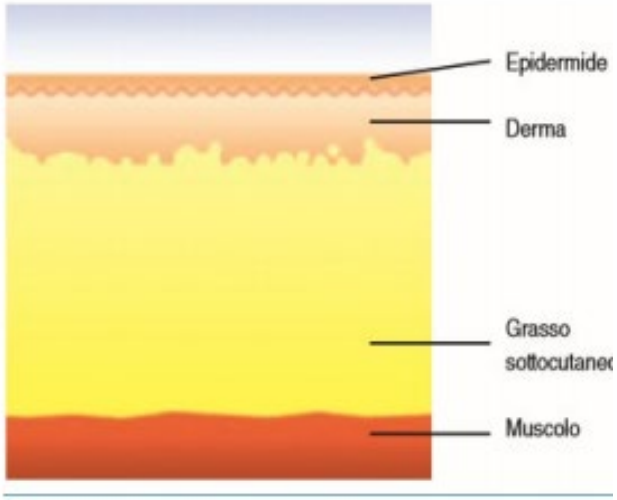


Media 38%
Variabili dal 2 al 75%

LIPOIPOTROFIA o LIPOATROFIA



Oggi < 5 %



LIPOHYPERTHOPHY PREVALENCE VARIABILITY

	Publication year	Prevalence (%)	Author	Diabetes type 1 or 2
Seyoum	1996	31.0	9	1 + 2
Hauner	1996	28.7	10	1
Partanen	2000	34.5	11	1
Raile	2001	27.1	12	1
Kordonouri	2002	48.0	13	1
Vardar	2007	48.8	14	1 + 2
Hajheydari	2011	14.5	15	1 + 2
Teft	2002	57.0	16	1 + 2
Blanco	2013	64.0	17	1 + 2
Grassi	2014	49.0	18	1 + 2
McNally	1988	28.0	19	2
Hauner	1996	3.6	10	2

Gentile S, et al. L A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes. Springerplus. 2016 May 5;5:563.

Le LIPO-IPERTROFIE variano dal 4,5% al 64%,

Ciò dipende da metodo, competenza e esperienza di chi le cerca

1 INSULTO MECCANICO RIPETUTO

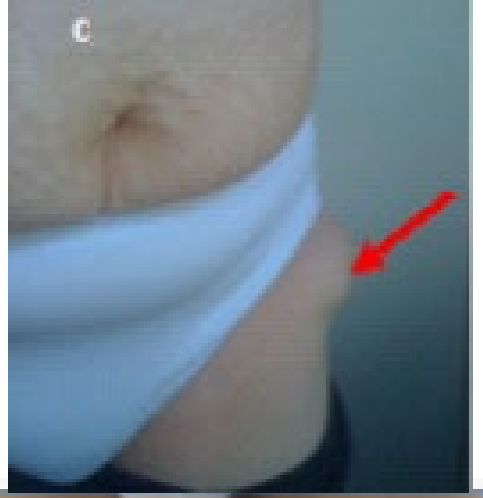
2 DENERVAZIONE CUTE

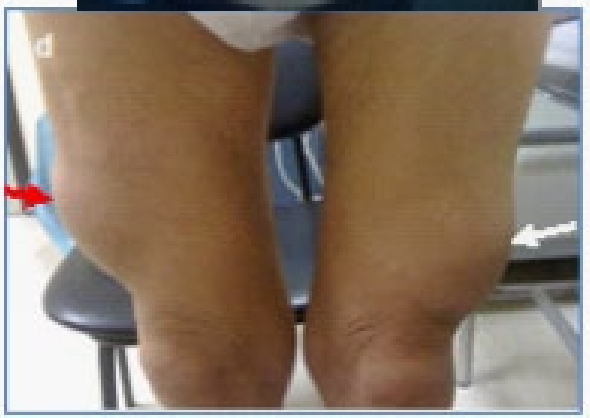
3 ASSENZA DI DOLORE REITERAZIONE

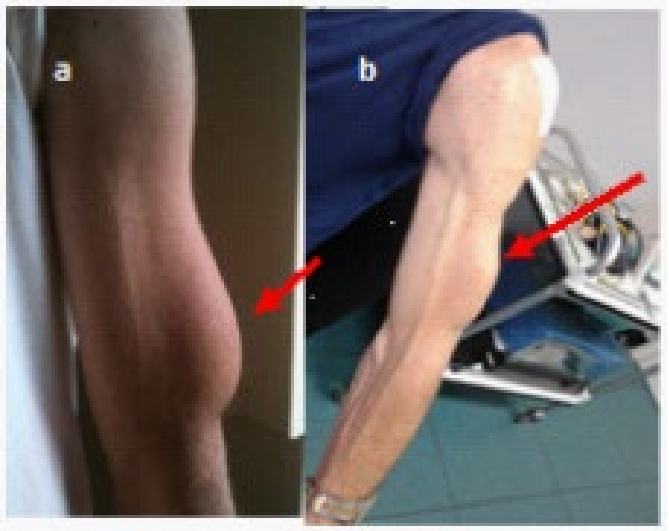
4 REAZIONE CUTE NODULO

5 ALTERATO ASSORBIMENTO INULINA

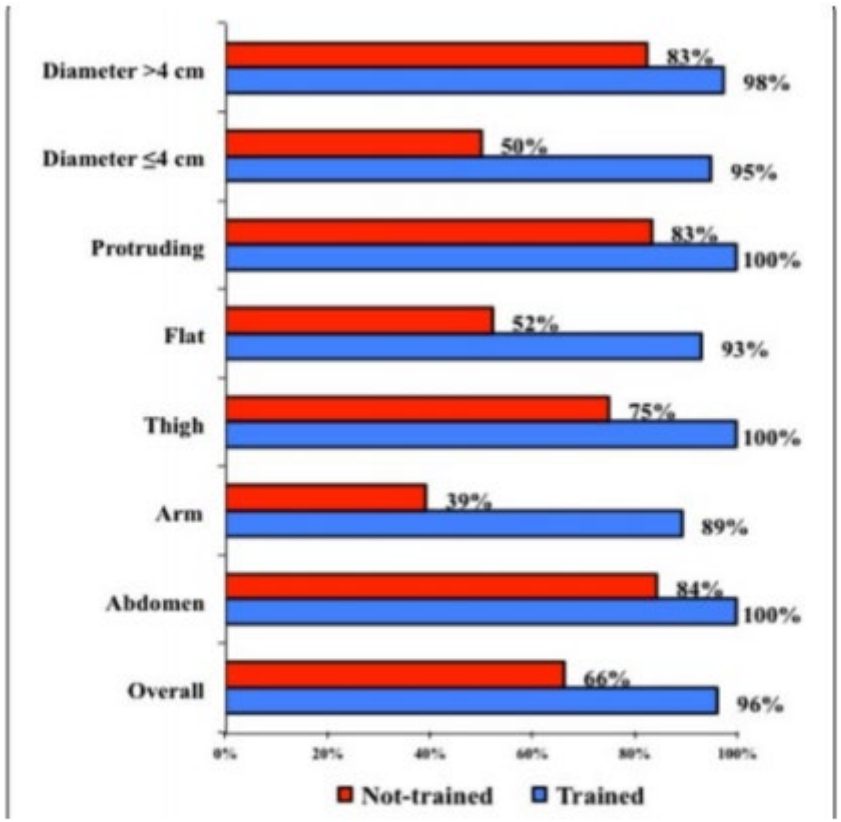
6 ALTA VARIABILTÀ GLICEMICA E IPOGLIEMIE INATTESE



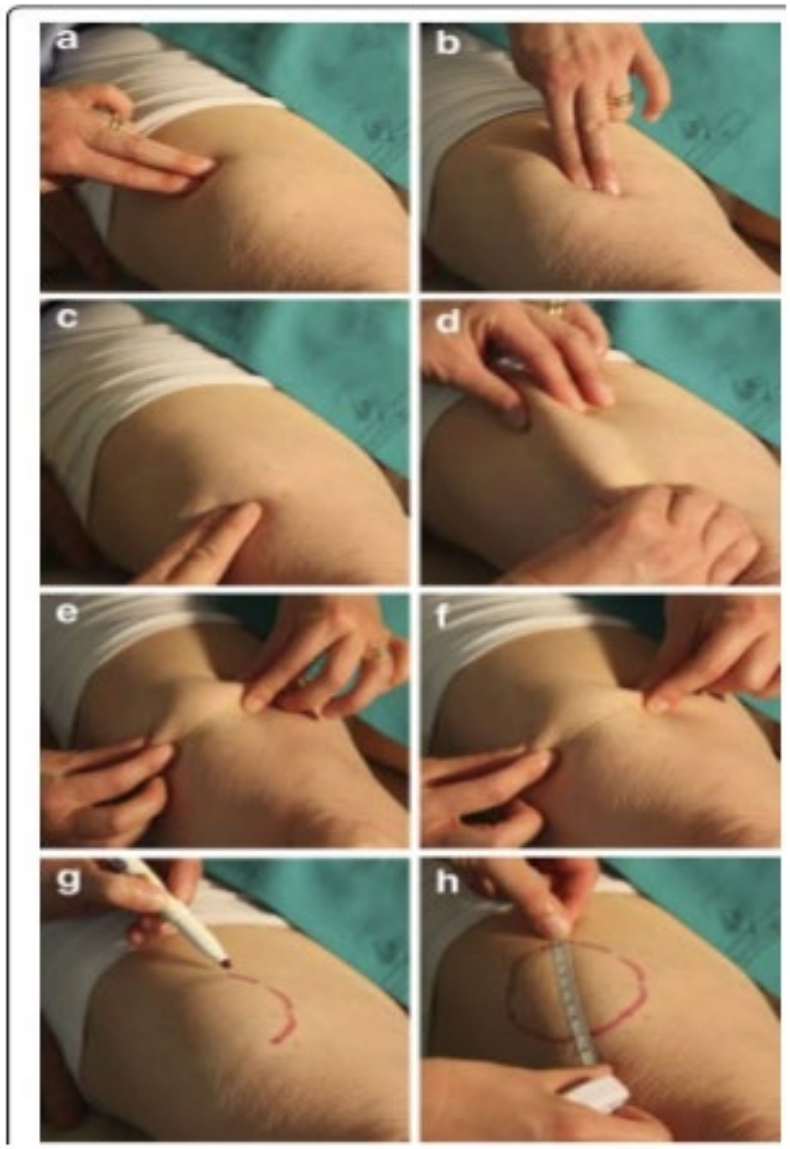




RICERCA DELLE LIPO-IPERTROFIE: METODOLOGIA

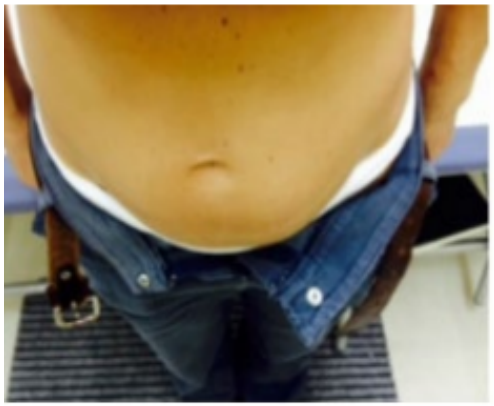


Lipohypertrophy identification results obtained by trained and non-trained health professionals as referred to the shape, site and size of skin lesions



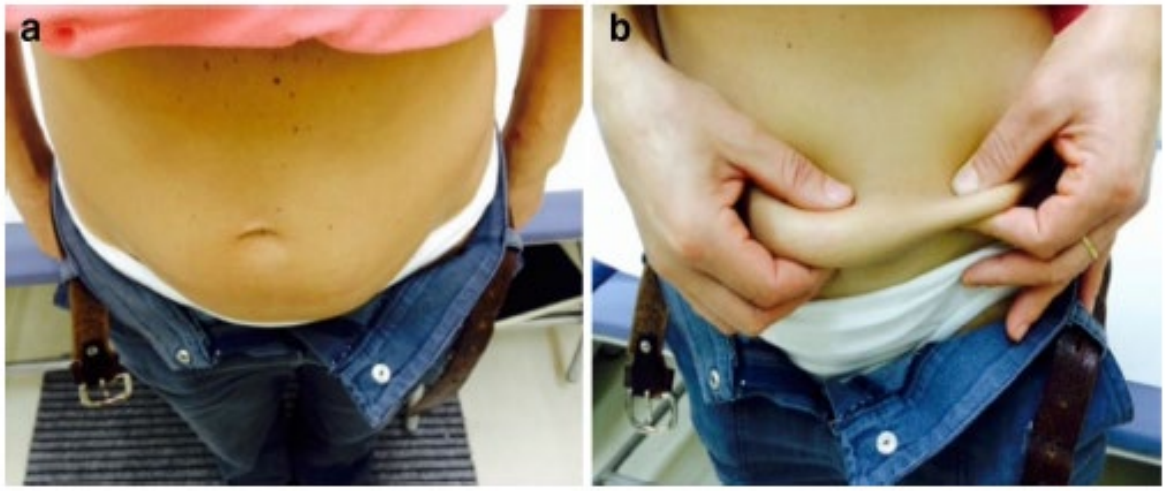
Gentile S, et al. A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes. Springerplus. 2016 May 5;5:563.

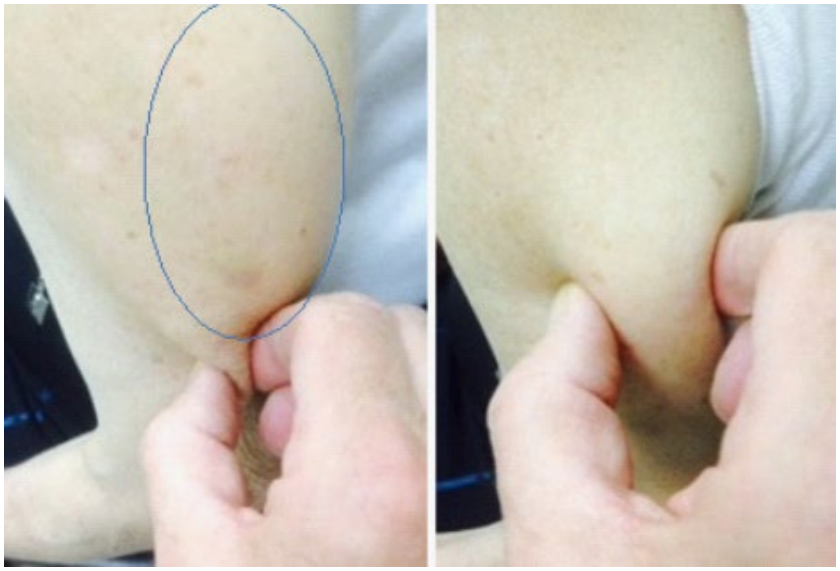
LIPOIPERTROFIA



Descritta come noduli sporgenti o piani di tessuto di consistenza duro gommosa, più o meno sporgenti sul piano della pelle circostante

PINCHING



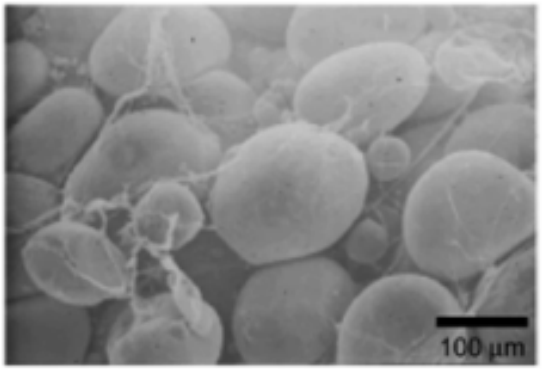


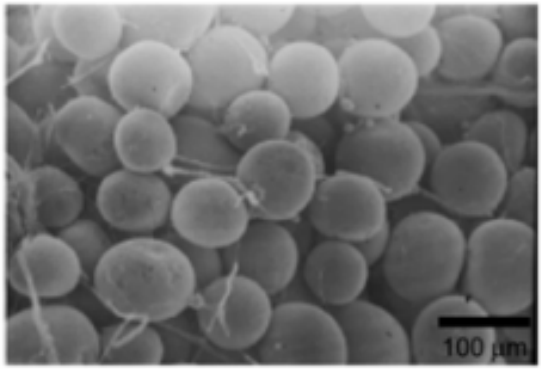
Gentile S, Grassi G, Armentano V, et al. AMD-OSDI Consensus on Injection Techniques for People with Diabetes Mellitus. Med Clin Rev. 2016, 2:3 doi: 10.21767/2471-299X.1000034

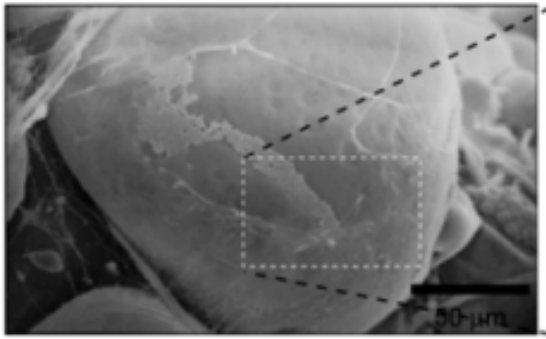
EFFETTI DELLE LIPODISTROFIE

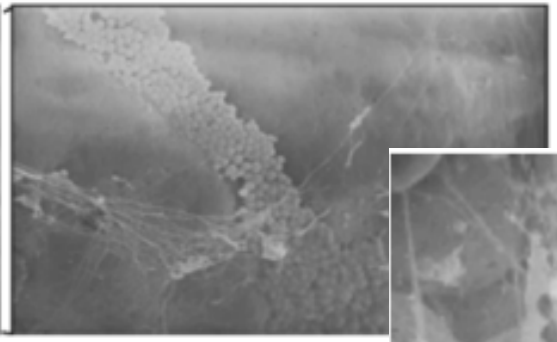
1. LH is very frequent
2. Main causes: insulin, non- rotation, reuse
3. LH distorts insulin absorption
4. LH worsens glucose control
5. LH leads to excessive and avoidable medical costs

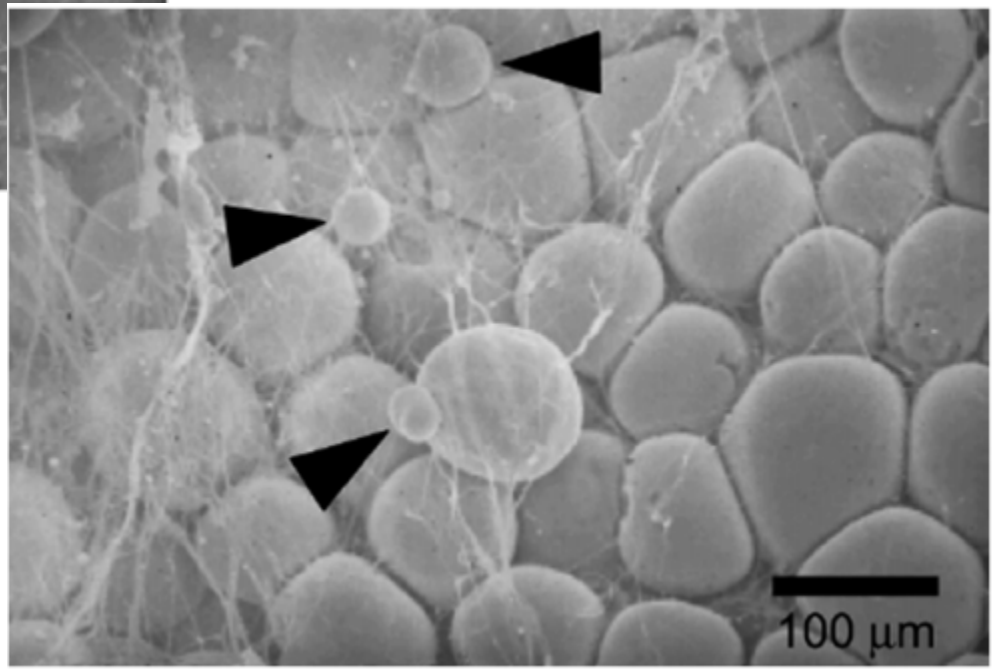
MICROSCOPIA ELETTRONICA DI NODULO LH
MEGA-ADICOPICI E MICRO-ADIPOCITI + AMPI TRALCI FIBROSI







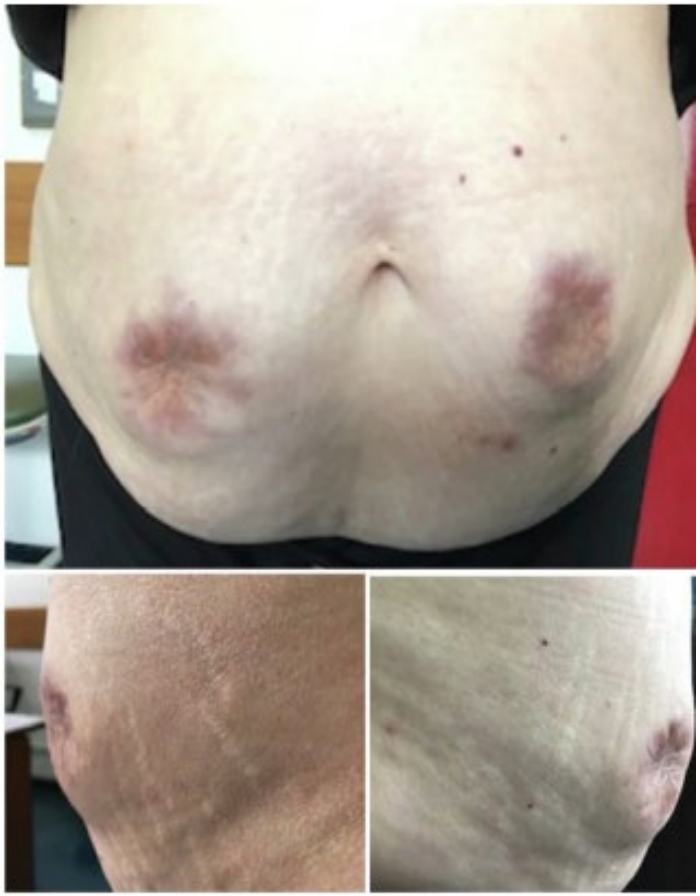


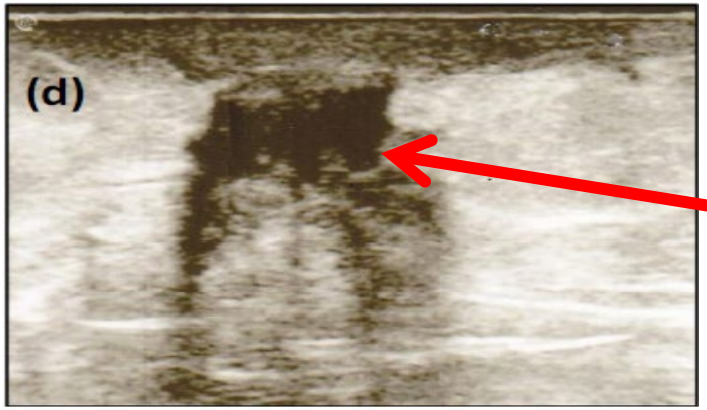


Rappresentazione schematica e caratteristiche clinico-morfologiche identificative dei tipi più frequenti di LH

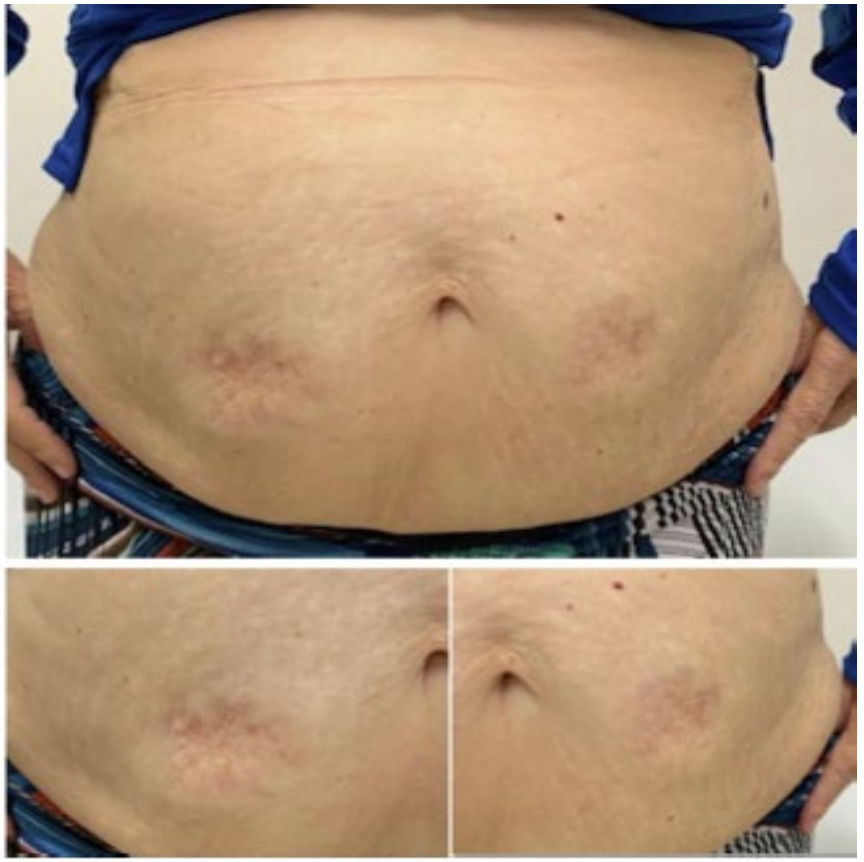
Tipo	Definizione	Visibilità	Palpabilità	Consistenza
A	Piccoli noduli	Facilmente evidente di profilo con luce tangenziale	Facile	Duro-elastica
B	Grandi noduli	Visibile di profilo, meglio con luce tangenziale	Facile	Duro-elastica
C	Piastrone duro-elastico	Visibile con difficoltà	Non facile/meglio definibile con pinching	Generalmente morbida
G	Nodulo molle	Non visibile	Difficile da distinguere/meglio con palpazione più vigorosa e/o pinching	Generalmente elastica

Gentile S, et al. L A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes. Springerplus. 2016 May 5;5:563.



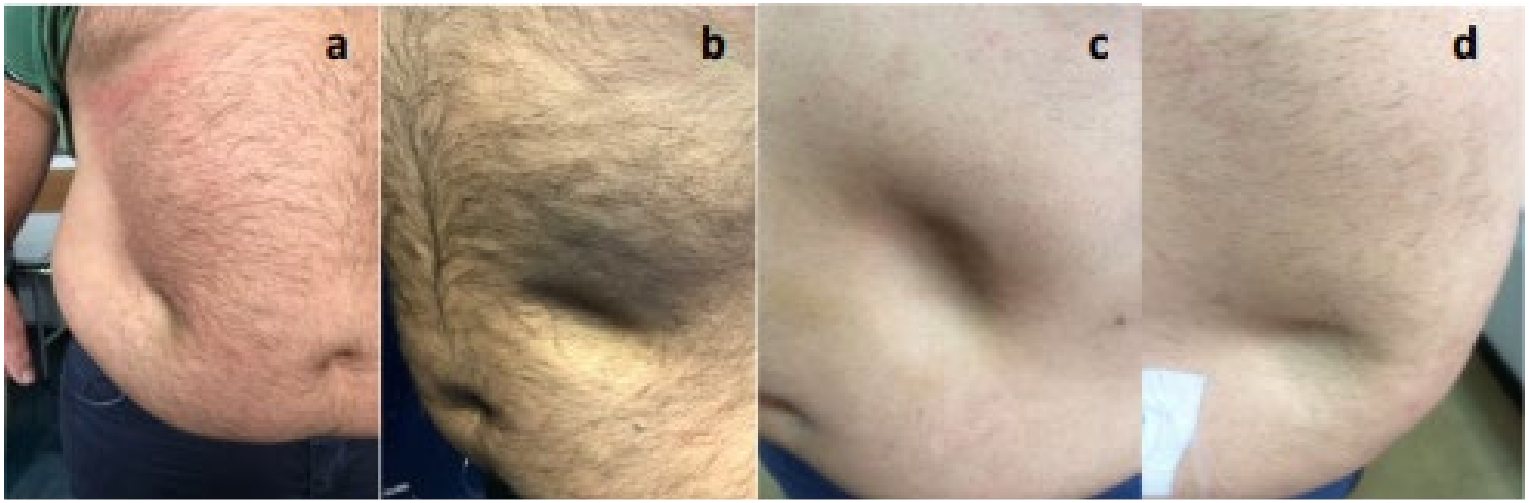


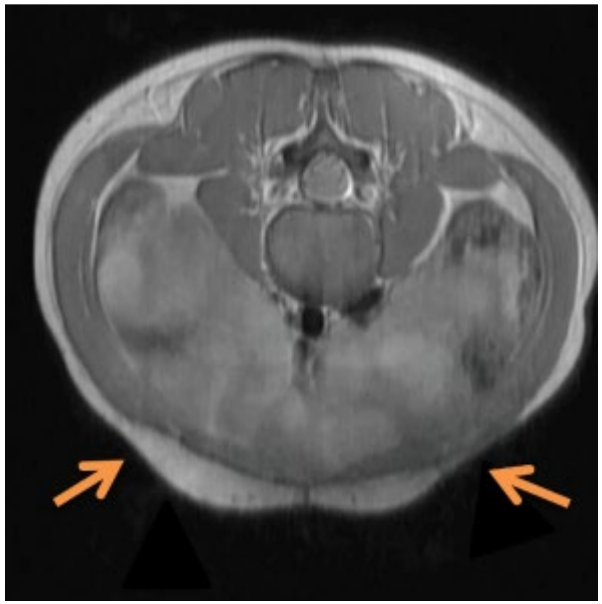
Tre anni dopo aver smesso di iniettare nei noduli



Liquido con insulina 13 volte più concentrata del sangue

Gentile et al. Diab Res Clin Pract 2021





Gentile et al. Diab Res Clin Pract 2018

Frequency of LH and diabetes complications

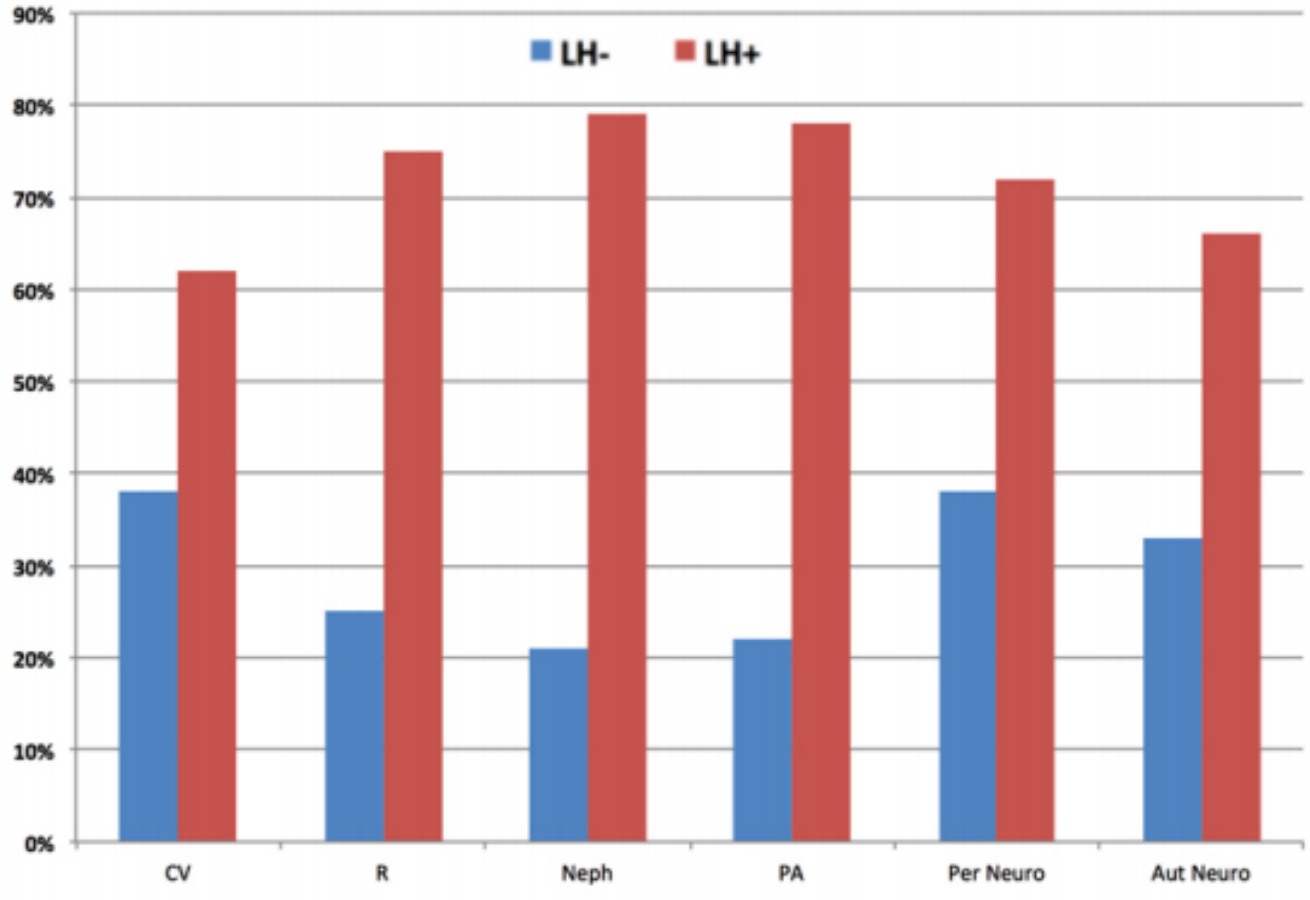


Figure 3: Frequency of LH and diabetes complications. All differences were statistically significant ($p<0.001$).
CV: Cardio-CerebroVascular complications; R: Retinopathy, Neph: Nephropathy; PA: Peripheral Artery disease; Per Neuro: Peripheral Neuropathy; Aut Neuro: Autonomic Neuropathy.

Gentile S. et al. Unexplained Hypoglycaemia and Large Glycaemic Variability: Skin Lipohypertrophy as a Predictive Sign. Diabetes Res Open J. 2016; 2(1): 24- 32. doi: 10.17140/DROJ-2-126

RELATIONSHIP BETWEEN NEEDLE LENGTH AND LIPOHYPERTROPHY

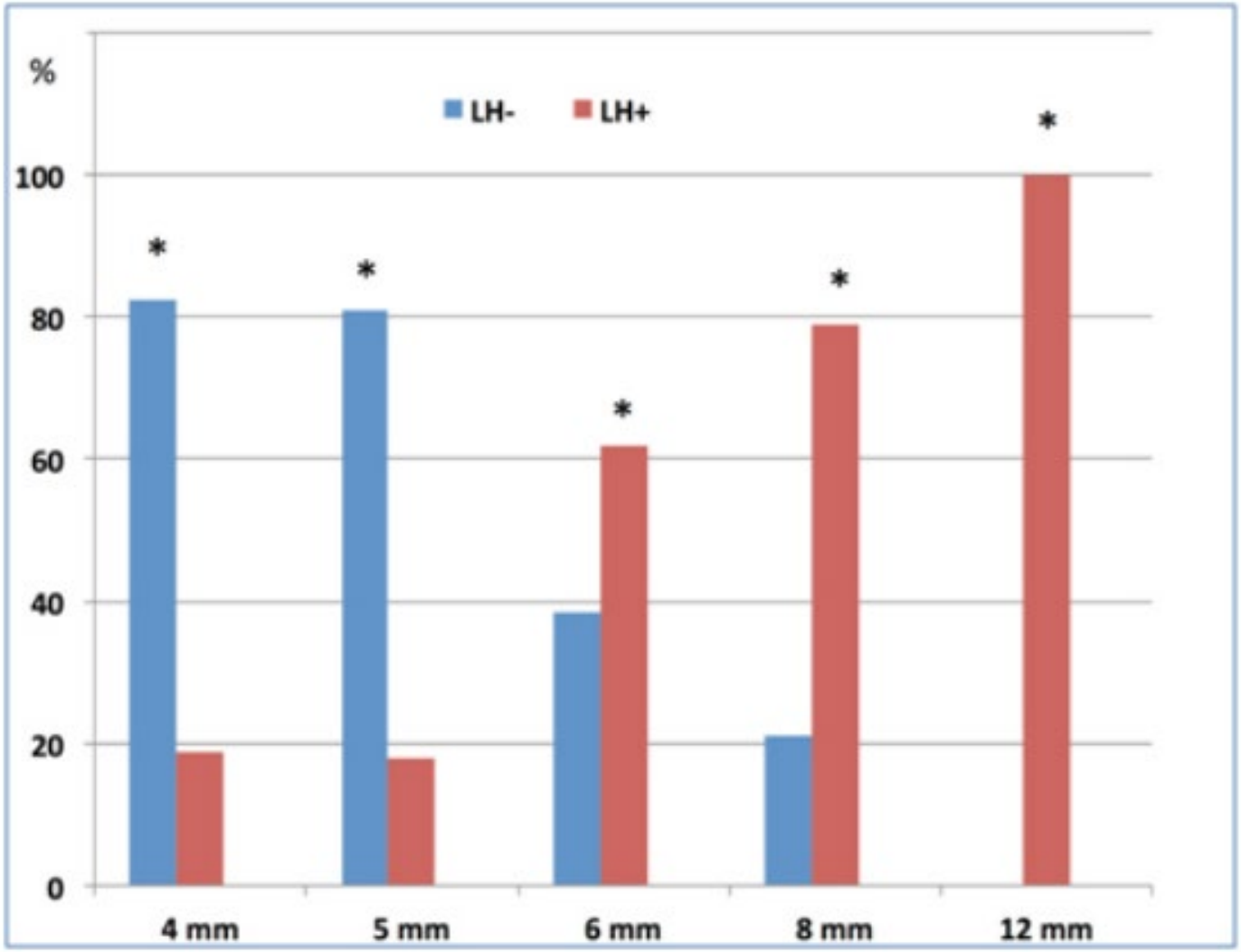


Figure 5: Relationship between needle length and lipohypertrophy. **p<0.001*

Gentile S. et al. Unexplained Hypoglycaemia and Large Glycaemic Variability: Skin Lipohypertrophy as a Predictive Sign. Diabetes Res Open J. 2016; 2(1): 24- 32. doi: 10.17140/DROJ-2-126

RELATIONSHIP BETWEEN NEEDLE GAUGE AND LIPOHYPERTROPHY

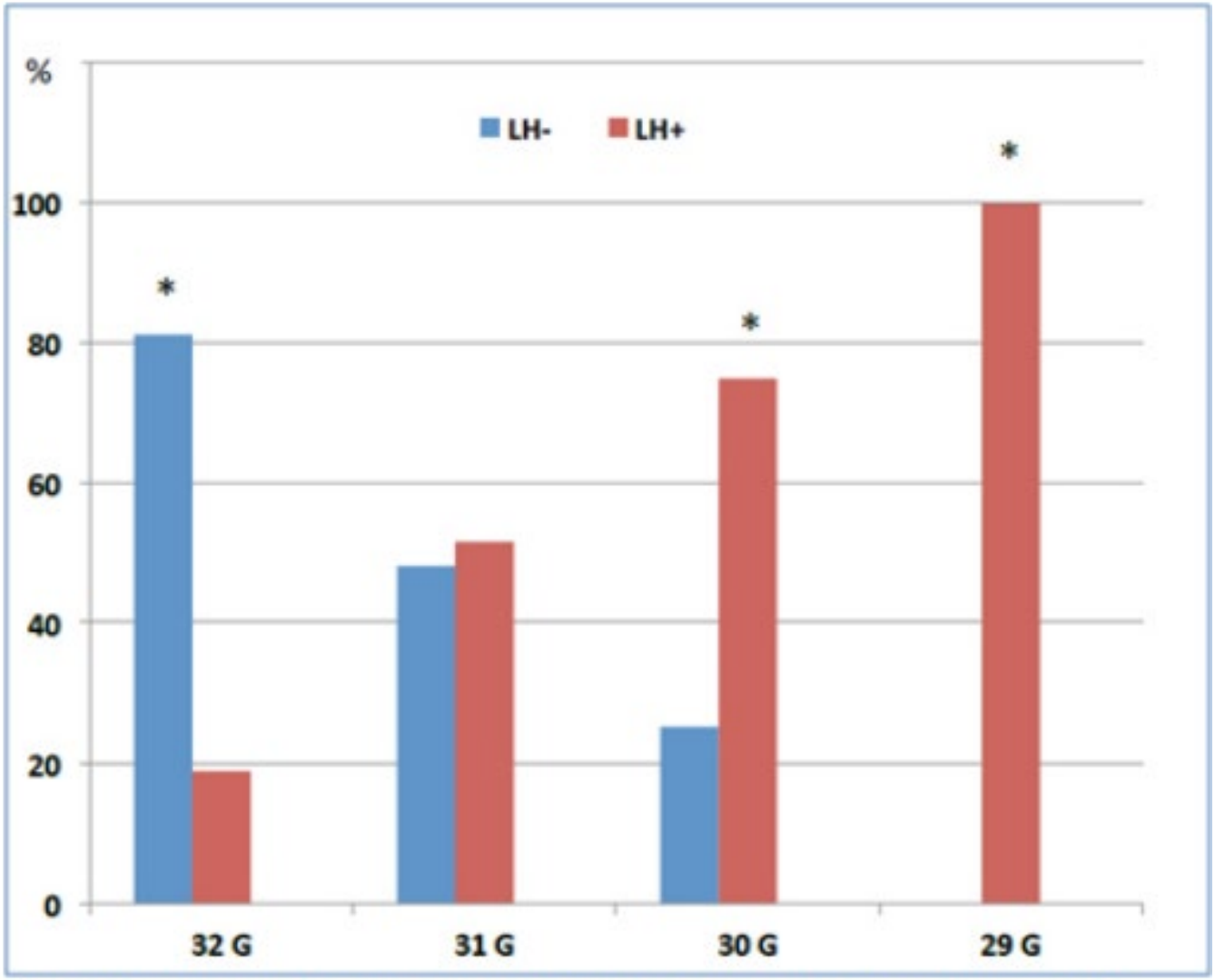
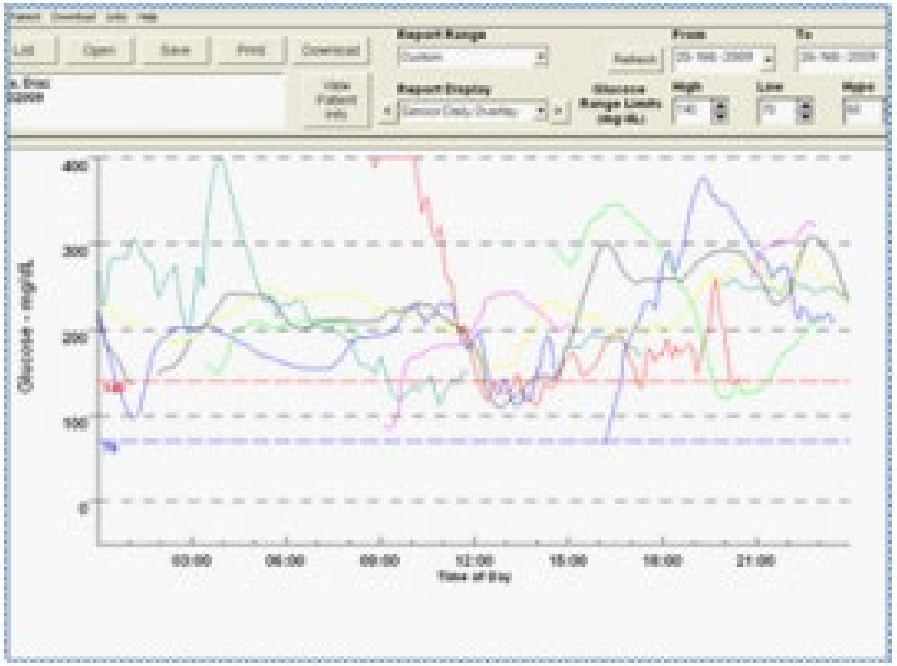
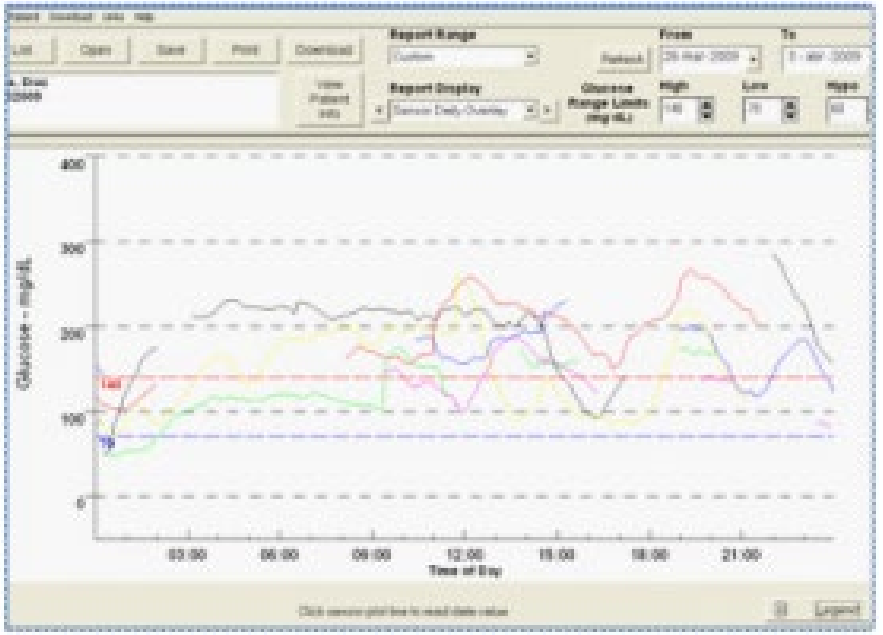


Figure 6: Relationship between needle gauge and lipohypertrophy. **p<0.001.*

Gentile S. et al. Unexplained Hypoglycaemia and Large Glycaemic Variability: Skin Lipohypertrophy as a Predictive Sign. Diabetes Res Open J. 2016; 2(1): 24- 32. doi: 10.17140/DROJ-2-126

VARIABILITÀ GLICEMICA





DIABETES RESEARCH AND CLINICAL PRACTICE 143 (2018) 320–321

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Cost saving effects of a short-term educational intervention entailing lower hypoglycaemic event rates in people with type 1 diabetes and lipo-hypertrophy

Sandro Gentile [a], *Felice Strollo* [b,*], *on behalf of the Nefrocenter Research Study Group*

198 persons T1DM and LH

Table 1 – Frequency and costs of severe and symptomatic hypoglycaemic events at baseline vs. post-education follow-up.

		Severe hypos (Sevs)				Symptomatic hypos (Syms)			
	Cost /event (€)	Baseline		Follow-up		Baseline		Follow-up	
		episodes n.	€	episodes n.	€	episodes n.	€	episodes n.	€
PHV	25.8	16	413.1	6*	154.9	0	0	0	0
ER	241.0	49	11809.0	18*	4338.0	0	0	0	0
EMS	128.5	49	6296.5	21*	2698.5	0	0	0	0
FM/CWD	78.6	136	10689.6	42*	3301.2	110	8646.0	42*	3301.2
DHC	750.0	13	9750.0	6*	4500.0	0	0	0	0
Total: €		38958.2		14992.6		8646.0		3301.2	

PHV = physician home visit; ER = emergency room visit and treatment; EMS = emergency medical service call/h; FM = family member; C = caregiver; WD = working day; DHC = daily hospitalization cost.

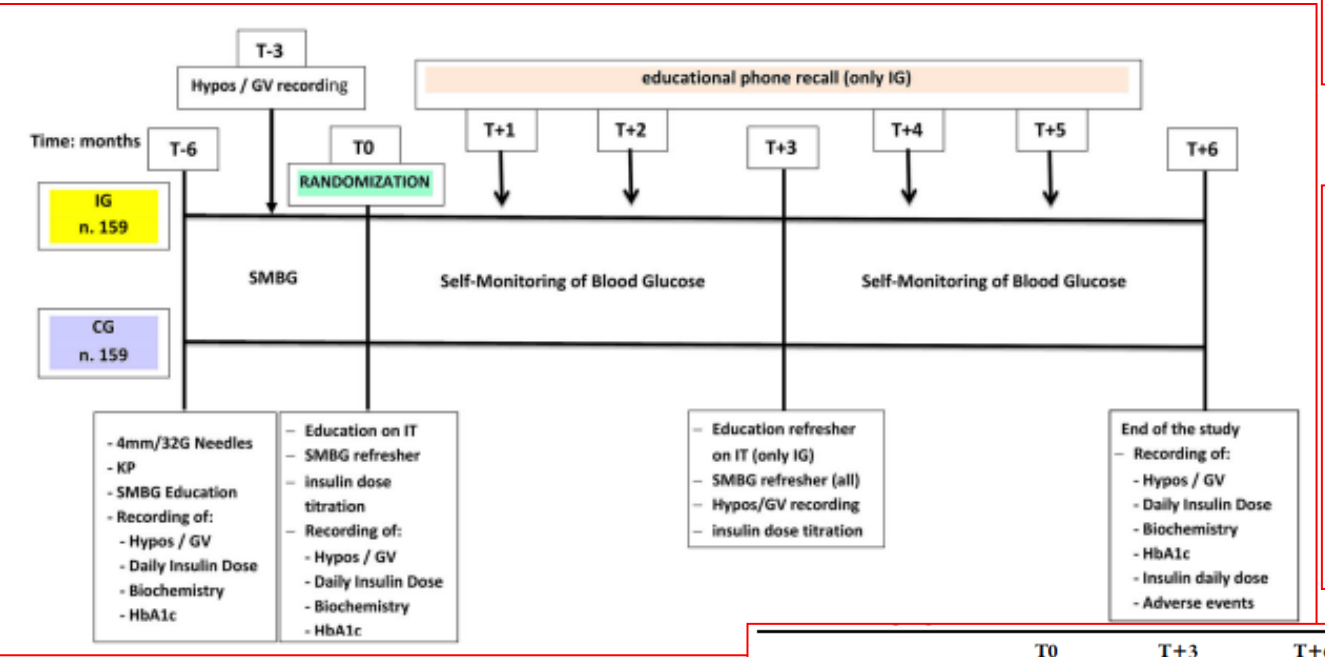
* $p < 0.01$ vs baseline.

Diabetes Ther
https://doi.org/10.1007/s13300-021-01006-0

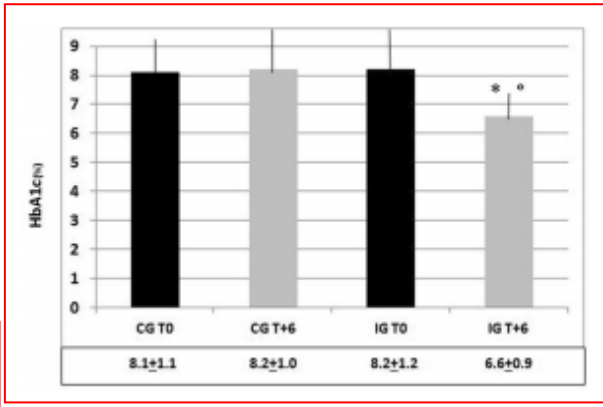
ORIGINAL RESEARCH

Gentile et al, 2020

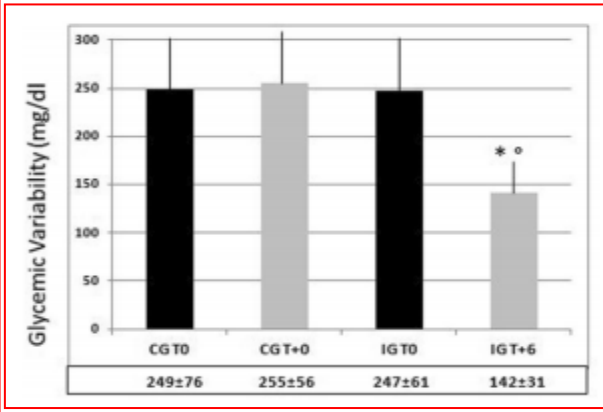
Role of Structured Education in Reducing Lypodistrophy and its Metabolic Complications in Insulin-Treated People with Type 2 Diabetes: A Randomized Multicenter Case–Control Study



HbA1c



Variabilità glicemica



↓ ipoglicemie

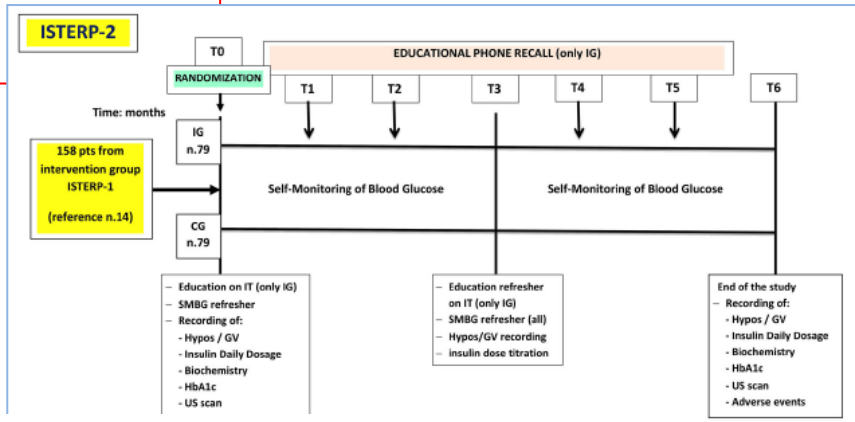
	T0 *n* = 159	T+3 *n* = 159	T+6 *n* = 159	Δ T0 vs T+6	*p* T0 vs T+6
Control group (*n* = 159)					
Severe hypo *n* (%)	26 (16.35)	20 (12.58)	22 (13.84)	− 4 (− 7.23)	n.s.
Symptomatic hypo *n* (%)	133 (83.65)	141 (88.68)	135 (84.91)	+ 2 (+ 1.51)	n.s.
Severe or symptomatic hypo *n*	159	159	153	− 6 (− 3.77)	n.s.
Intervention group (*n* = 159)					
Severe hypo *n* (%)	26 (16.35)	9 (5.66)[a]	1 (0.63)[a, c, d]	− 25 (− 96.15)[d]	0.0001
Symptomatic hypo *n* (%)	133 (83.65)	66 (41.51)[a, e]	12 (7.55)[a, d]	− 121 (− 90.97)[d]	0.0001
Severe or symptomatic hypo *n*	159	75[a, d]	13[a, c, d]	− 299 (− 91.82)[d]	0.0001

Diabetes Ther (2021) 12:2557–2569
https://doi.org/10.1007/s13300-021-01108-9

ORIGINAL RESEARCH

Gentile et al, 2021

The Durability of an Intensive, Structured Education-Based Rehabilitation Protocol for Best Insulin Injection Practice: The ISTERP-2 Study



Frequency of severe and symptomatic hypoglycemic events

Study groups	Hypoglycemic episodes	T0 (n = 158 overall)	T+3 (n = 79)	T+6 (n = 79)	Δ T+6 increase/ decrease vs. T0 (n times)	p
Control group (n = 79)	Severe	1 (1.26)	5 (6.32)*	9 (11.39)	+ 9.0	0.00134
	Symptomatic	6 (7.59)	14 (17.72)**	24 (30.37)	+ 4.0	0.0198
	Overall	8 (10.12)	19 (24.05)**	33 (41.77)	+ 4.12	0.0189
Intervention Group (n = 79)	Severe	0	0	0	–	–
	Symptomatic	6 (7.59)	2 (2.53)*	3 (3.79)	− 0.5	0.05
	Overall	6 (7.59)	2 (2.53)*	3 (3.79)	− 0.5	0.05
	Symptomatic control group vs. intervention group	n.s	0.00128	0.00192		

FACCIAMO INSIEME UN PICCOLO TEST

HAI PAZIENTI CON LIPOIPERTOFIE?

FACCIAMO INSIEME UN PICCOLO TEST

CONTROLLI SISTEMATICAMENTE LE SEDI INIETTIVE ALLA RICERCA DI LIPODISTROFIE ?

CON QUALE FREQUENZA LO FAI?

1. **AD OGNI VISITA ?**
2. **OGNI 6 MESI ?**
3. **1 VOLTA ALL'ANNO DURANTE LO SCREENING DELLE COMPLICANZE ?**


Thank you
Tak
Kiitos
Ευχαριστώ
Dziękuję
Hvala
谢谢
Obrigado
Merci
Danke
Tack
תודה
Gracias
Thank you
Grazie
شكرا
謝謝
감사합니다
ありがとう
Спасибі